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EXAMINER

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1636

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

DETAILED ACTION

This US Application 10/577,778, filed 8 January 2007, which is a 371 of PCT/GB04/04560, filed 28 October 2004, claims foreign priority to GB0325085.9, filed 28 October 2003. Applicant's submission filed 4/22/2011 is acknowledged. Claims 4-10 and 13-14 are cancelled. Claims 1-3 and 11-12 are pending and under examination.

Response to Amendments

All rejections to cancelled claim 13 are moot.

The rejection of Claims 2 and 3 under 35 U.S.C. 112(second paragraph) is withdrawn based on claim amendments.

The rejection of Claims 1-3 and 11-12 under 35 U.S.C. 102(b) as being anticipated by Baillie et al is withdrawn based on claim amendments.

The rejection of Claim 1 under 35 U.S.C. 102(b) as being anticipated by Gorfien et al is withdrawn based on the Applicants' following persuasive argument: Regarding the anticipation rejection of Claim 1 by Gorfien et al, the Applicants argue on page 6 of Remarks filed 4/22/2011 that "the cyclodextrin-cholesterol supplement of the Gorfien et al reference is not encompassed by Applicants' definition of 'sLDL particle' ".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3 and 11-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Baillie et al** in “A synthetic low density lipoprotein particle capable of supporting U937 proliferation in vitro” (J of Lipid Research, Vol., 43, No. 1 January 2002, page 69-73; whole document, of record), in view of **Mainwaring and Wayte**, in “Cell Culture Medium” (US Patent 7,258,998 filed 24 November 2004 with priority to US Provisional 60/411,751 filed on 19 September 2002; of record) and further in view of **Gorfien et al** in “Growth of NSO cells in protein-free, chemically defined medium” (Biotechnology Progress, September 2000, Vol. 16, No.5, pages 682-687; whole document, of record). *This is a new grounds of rejection necessitated by amendment.*

Currently amended claim 1 is drawn to a method of proliferating eukaryotic NSO cells, comprising the step of introducing synthetic low density lipoprotein (sLDL) particles to an NSO cell culture and allowing cells in the culture to proliferate, wherein the NSO cell culture lacks

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foetal calf serum (FCS). Claim 2 specifies that the sLDL particles are peptide free and that culturing NSO cells in the presence of the peptide-free sLDL particles increases NSO cell proliferation by at least 20% relative to NSO cells cultured in the absence of the sLDL particles and in the presence of foetal calf serum (FCS) or other serum-free lipid supplements. Claim 3 specifies that the sLDL particles comprise a peptide and wherein culturing NSO cells in the presence of the sLDL particles comprising a peptide increases NSO cell proliferation by at least 50% relative to NSO cells cultured in the absence of the sLDL particles comprising the peptide and in the presence of foetal calf serum (FCS) or other serum-free lipid supplements. Claim 11 depends from claim 1 and specifies that the sLDL particles comprise cholesterol and/or cholesterol ester, and that a total concentration of the cholesterol and cholesterol ester is greater than 0.009 mg/ml of a culture medium. Claim 12 depends from claim 11 and specifies that the total concentration of the cholesterol is greater than 0.018 mg/ml of the culture medium.

Baille et al teach a method of proliferating mammalian U937 lymphoma cells by adding synthetic low density lipoprotein (sLDL) particles to a cell culture and allowing cells in the culture to proliferate (e.g. see Title and abstract). Baille et al report preparing sLDL particles with and without peptides and show a comparison of cells grown without sLDL particles *versus* cells grown with sLDL (with and without peptides) and show at least a 20% increase in cell growth using sLDL particles without peptides and show at least a 50% increase in cell growth using sLDL particles with peptides (e.g. see page 71, Figure 1 and 2 and legends). On page 71, left column (under “Results”), Baille et al disclose that “to determine if sLDL could also support increases in U937 cell numbers, the cells were incubated with PEP1sLDL at a cholesterol concentration (80 μ mol/l) equivalent to FCS supplementation”. Since 80 μ mol/l cholesterol

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calculates to approximately 0.03096 mg/ml, Baille et al reads on wherein “the sLDL particles comprise cholesterol and/or cholesterol ester, and that a total concentration of the cholesterol and cholesterol ester is greater than 0.009 mg/ml of a culture medium” and that “the total concentration of the cholesterol is greater than 0.018 mg/ml of the culture medium”.

However, although Baille et al teach the use of a mammalian lymphoma cell line (U937 cells) that is unable to perform de novo cholesterol synthesis and thus has a requirement for an extracellular cholesterol source, Baille et al fail to explicitly teach NSO cells.

It would have been obvious to one of ordinary skill in the art to substitute NSO cells for U937 cells in the cell proliferation methods of Baille et al because both Mainwaring et al and Gorfien et al disclose NSO cells as preferred cells for culture medium lacking fetal calf serum. For example, **Mainwaring et al** disclose that NSO cells are plasmacytomas and are in consequence of B-lymphocytic lymphoid cell lineage as are hybridomas (column 5, lines 21-29). Mainwaring et al disclose that protein-free culture media are particularly preferred in conjunction with the use of myeloma cell lines such as NSO (column 6, lines 61-63). Mainwaring et al disclose NSO cells are a preferred cell and that culture medium lacking fetal calf serum is a preferred medium (column 6, lines 18-20). Mainwaring et al disclose that NSO cell lines are a preferred cell line for cell culture medium studies and that “most NSO cell lines are cholesterol-dependent, usually making cholesterol an obligate component of the culture medium”, (column 5, lines 36-37) and stating the NSO cell lines are “freely available from the European Collection of Cell Cultures” (column 5, lines 21-29). In addition, **Gorfien et al** teach a method of proliferating NSO cells by adding synthetic low density lipoprotein (synthetic LDL) particles to a cell culture and allowing cells in the culture to proliferate (e.g. see Title, abstract and page 683

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especially under Heading: "Additive Options". Gorfien et al teach that "many hybridomas and recombinant myeloma cell lines have been successfully adapted to growth in protein-free media" (abstract, lines 1-2). Gorfien et al recite: "NSO is a nonimmunoglobulin secreting, nonlight chain synthesizing subclone of NS-1 that has traditionally been cultured in RPMI 1640 + 2 mM L-glutamine + 10% FBS" and continue that NSO cells are useful for recombinant expression systems (page 682, first paragraph). Gorfien et al disclose that "[a]s NSO cells have become more popular for large-scale expression of recombinant proteins, removal of serum from the culture system has become a priority" (page 682, paragraph 1, lines 6-9).

One would have been motivated to use NSO cells as disclosed in both Mainwaring et al and Gorfien et al in substitution for U937 cells used in the method of Baille et al because Mainwaring et al disclose that NSO cells have been found to give potentially rise to extremely high product yields, and state that most standard NSO cell lines are cholesterol-dependent, usually making cholesterol an obligate component of the culture medium (e.g. column 5, lines 21-38). In addition, Gorfien et al disclose that "[a]s NSO cells have become more popular for large-scale expression of recombinant proteins, removal of serum from the culture system has become a priority" (page 682, paragraph 1, lines 6-9).

Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, being at the level of an MD or PhD research scientist, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

In view of the foregoing, the method of claim 1-3 and 11-12, as a whole, would have

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been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC §103(a).

Response to Arguments: Applicants' response (Remarks filed on 4/22/2011) has been fully considered. Although the rejection above is a new grounds of rejection necessitated by amendment, the applicants' arguments which are pertinent to the new grounds of rejection are addressed herein. Applicant argues (e.g., starting on page 6 of Remarks, last paragraph) that it would not have been obvious to one of ordinary skill in the art to use NSO cells as disclosed in Mainwaring in place of U937 cells described in Baillie et al. Specifically, Applicants argue that Baillie et al only teach methods of proliferating U937 cells and do not suggest using any other cell type, including NSO cells while Mainwaring et al do not suggest supplementing serum-free media with cholesterol via sLDL particles. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In addition, Applicants' argument that the combination of Baille et al and Mainwaring et al fail to provide the skilled artisan with a reasonable likelihood of success in developing the presently claimed invention is not persuasive for reasons provided above and particularly because Mainwaring et al disclose that NSO cells have been found to give potentially rise to extremely high product yields, and state that most standard NSO cell lines are cholesterol-dependent, usually making cholesterol an obligate component of the culture medium (e.g. column 5, lines 21-38).

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Conclusion

No claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Catherine Hibbert whose telephone number is (571)270-3053.

The examiner can normally be reached on M-F 8AM-5PM, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/NANCY VOGEL/

Primary Examiner, Art Unit 1636

Catherine Hibbert

Examiner AU1636